Institute of Neurology
(Queen Square)
University College London

NEURAL & BEHAVIOURAL DIFFERENCES BETWEEN SUBGROUPS OF SUBJECTS WITH DYSLEXIA

Benedetta Monzani, BSc

MSc Clinical Neuroscience
2007-2008

Supervisor: Professor Cathy Price

Wellcome Department of Imaging Neuroscience
The Institute of Neurology
University College London

Submitted as partial fulfilment of the requirements for the MSc in Clinical Neuroscience, University of London

Year of Submission: July 31st, 2008
Word Count: 9,489

ACKNOWLEDGEMENTS

I sincerely like to express many thanks to Professor Cathy Price for her admirable charismatic attitude for her job and with her students, continued support and help round the clock as well as for her talent in creating a rewarding and stimulating environment throughout the research project. Thank you for giving me the opportunity to work on this project and for your patience while helping me.

Many thanks also to Fiona Richardson for her availability and helpful comments during data analysis and to Ferath Kherif for finding the time and patience to clarify the process behind Principle Component Analysis and the Gaussian Mixture Modelling.

STATEMENT OF CONTRIBUTORS

Study Design	Supervisor Professor Cathy Price
Data Collection	Supervisor Professor Cathy Price
	Yaqub Al Sami
	Goulven Josse
	Benedetta Monzani
	Alex Peters
	Sue Ramsden
Data Analysis	Supervisor Professor Cathy Price
	Ferath Kherif
	Benedetta Monzani
	Fiona Richardson
Write Up	Benedetta Monzani

ABBREVIATIONS

AC	Accuracy
ANOVA	Analysis of Variance
D1	Subgroup of dyslexic reader # 1
D2	Subgroup of dyslexic reader # 2
D3	Subgroup of dyslexic reader # 3
DD	Developmental dyslexia
DTI	Diffusion Tensor Imaging
fMRI	Functional Magnetic Resonance Imaging
FSIQ	Full scale Intelligence Quotient
GMM	Gaussian Mixture Modelling
NI	Non-impaired readers
O-T	Occipito-temporal
PALPA	Psycholinguistic Assessment of Linguistic Processing in Aphasia
PCA	Principle Component Analysis
PET	Positron Emission Tomography
PhAB	Phonological Assessment Battery
PIQ	Performance Intelligence Quotient
RT	Reaction time
STG	Superior Temporal Gyrus
T-P	Temporo-parietal
VBM	Voxel-Based Morphometry
VIQ	Verbal Intelligence Quotient
WAIS	Wechsler Adult Intelligence Scale III
WRAT	Wide Range Achievement Test

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

TABLES

FIGURES

APPENDIX

ABSTRACT

A literature review on neuroimaging research on developmental dyslexia (DD) highlights inconsistencies regarding the structural and functional abnormalities underling the disorder. The discrepancies in findings have been partly attributed to the heterogeneity of DD, thus instigating researchers to study whether the disorder can be categorized into different subtypes, reflecting distinct neural and behavioural phenotypes.

The following fMRI study was conducted to identify subgroups of dyslexics on the basis of their brain activation for reading aloud by using an unbiased classification method (PCA/GMM). The study then aimed to establish structural and behavioural differences distinguishing the subgroups. Thirty-four subjects with dyslexia and 34 non-impaired readers were scanned using fMRI and assessed using varies psychometric tests. A one sample t-test was used to add together functional images from subjects and treat the inter-subject variability as error variance. PCA and GMM then allowed the identification of subgroups and assignment of subjects to the groups, while statistical analyses highlighted brain activation and behavioural differences between the subgroups.

Three subgroups of dyslexics (D1, D2, and D3) were identified. Results showed that D1 overactivated bilateral superior temporal gyri; whereas D2 and D3 showed abnormal underactivations in 3 areas (bilateral temporo-parietal cortex, left occipito-temporal cortex, and cerebellum). D3 also tended to perform worse on most psychometric tests, and statistically worse on auditory short term memory tasks. Findings of differences in activation patterns and behavioural performance between the subgroups dyslexic may support the existence of subtypes of dyslexia, where one subgroup reflects compensated dyslexics while the another is characterized by auditory short term memory deficits.

I. INTRODUCTION

The goal of the following introduction is to provide the reader with a basic knowledge and general overview of dyslexia. In order to clearly and concisely describe this neuro-behavioural condition and the background instigating the present research project, the introduction has been subdivided into three parts: 1) overview of dyslexia; 2) review of neuroimaging research on dyslexia, with an emphasis on functional and structural imaging, as well as inconsistencies of findings; and also 3) a review of the literature on subgrouping individuals with dyslexia.

1) Overview of Dyslexia

Dyslexia derives from the Greek word *dys-*, meaning "impaired", and *lexis* meaning "word". Dyslexia is a specific learning disability that manifests itself as a difficulty with reading and spelling in individuals with average or above average intellectual abilities. It is characterized by deficits in recognizing, decoding, and spelling words, thus affecting reading accuracy and fluency (Shaywitz et al., 2003).

Dyslexia was first noted in 1887 by Rudolf Berlin when describing a case of a young boy of average intelligence affected by a severe impairment in reading. The disorder began to be recognized and then termed "word blindness" by Pringle Morgan in 1986, date after which research on dyslexia began to become more prominent (Shaywitz et al., 2003).

In terms of prevalence and features, epidemiological studies show that dyslexia is one of the most common neuro-behavioural disorders, equally affecting boys and girls with prevalence between 5 to 17.5% (Interagency Committee on Leaning Disability 1987; Shaywitz 1998). Dyslexia is also a persistent, chronic and heterogeneous condition (Shaywitz et al., 2003) as well as a familial and heritable disorder. Shaywitz et al. (1998) in fact found that 23% to 65% of children of parents with dyslexia have the disorder as well as 40% of siblings of dyslexics. Twin studies have furthermore shown a greater concordance rate for dyslexia among monozygotic twins (68%) than among dizygotic twins (38%) (Francks et al., 2002). Lastly in terms of the general aspects of dyslexia, affected individuals often show abnormalities and impairments not only in reading and spelling, but also in non-reading domains, including speech, visual, tactile and hearing impairments, writing shortfalls, short term memory skills, and motor skills deficits (Ramus et al., 2003).

Several theories attempt to explain dyslexia by approaching the topic from different perspectives and backgrounds. The *phonological theory*, currently receiving the greatest support among researchers, postulates that the core deficit of individuals with dyslexia is in phonological processing. The theory is based on the idea that reading requires learning the grapheme-phoneme correspondence, specifically learning that letters correspond to precise sounds. The phonological theory is supported by evidence for poor performance of dyslexics on phonological tasks, poor verbal short-term memory and impaired automatic naming skills. Evidence also arises from anatomical and imaging studies, supporting the view for a deficit in regions that are associated with phonological processing (Ramus et al., 2003).

Other theories on dyslexia include the *rapid auditory processing theory*, sustaining auditory deficits causing phonological, thus reading, impairments in dyslexia; the *visual theory*, supporting visual impairments in the magnocellular system to be responsible for the difficulties in reading letter and words; the *cerebellar theory* claiming that cerebellar anomalies lead to impaired articulation and phonological representations as well as impaired automatization skills; and finally, the *magnocellular theory*, an integrated theory on DD sustaining a dysfunction in the magnocellular pathway affecting the visual, auditory and tactile systems and explaining the cerebellar alterations found in dyslexics in terms of the connections between the magnocellular system and the cerebellum. Therefore, the theory accounts for the visual, auditory, tactile, motor, and phonological deficits that have been reported over the centuries of research on dyslexia. Although, there are a number of weaknesses that have been raised for each model (Ramus et al., 2003), all of them point to important factors which may not be exclusive of each other and may even represent different subtypes of dyslexia (Ramus et al., 2003).

In conclusion, DD is a common disability affecting reading fluency and accuracy in individuals with otherwise average or above average intelligence. An agreement among researchers views DD as a prevalent and lifelong condition, presenting a core deficit at a phonological processing level. Since 1986 increasing attention has been devoted to the study of dyslexia and with the advent of neuroimaging more is to come.

2) Literature review of neuroimaging research on dyslexia:

Current research on dyslexia is strongly focused on studying the neural basis underlying the disorder. The majority of neuroimaging studies investigating brain anomalies in dyslexia rely on methods consisting of either a comparison between dyslexic and non-impaired readers or between two groups of dyslexics following a subdivision based on behavioural performances (e.g. compensated versus persistently impaired dyslexics, surface dyslexics versus phonological dyslexics, etc.) or based on other factors (e.g. socio-economic status). Independent of the methods and approaches used, neuroimaging studies have drawn attention to different brain regions involved in dyslexia. The following paragraphs will provide an up to date review of the most relevant *a)* functional and *b)* structural imaging studies on dyslexia, as well as a review of the *c)* limitations and inconsistencies in neuroimaging research on dyslexia.

a. Functional imaging studies on dyslexia

The functional imaging studies reviewed below include positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) experiements on dyslexia. Despite controversy regarding the areas involved in dyslexia and the interpretation of the results, converging evidence indicates the functional involvement of at least three regions in dyslexia located in the left hemisphere: 1) left inferior frontal region; 2) temporo-parietal system involving angular gyrus, supramarginal gyrus and posterior portions of the superior temporal gyrus; and the 3) occipito-temporal system involving portions of the middle temporal gyrus and middle occipital gyrus (Shaywitz et al. 2002).

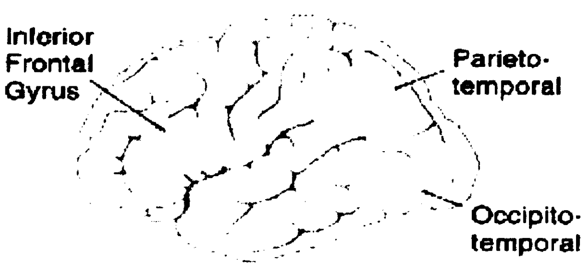

Figure 1. Neural systems for reading (Adopted from Shaywitz et al., 2003)

When comparing dyslexic to non-impaired readers during reading tasks, a significant number of functional studies have disclosed underactivations in the temporo-parietal cortex (Hoeft et al., 2006; Meyler et al., 2007; Rumsey et al., 1997, 1998, 1999; Shawitz et al., 2002), while many other have also highlighted underactivations in the occipital-temporal cortex, including the posterior middle temporal cortex and the inferior fusiform area (Brambati et al., 2006; Brunswick et al., 1999; Hoeft et al., 2007; McCroy et al., 2004; Shaywitz et al., 2003; Shaywitz et al., 2007). Many of the functional deficits in these regions have been found both in adults and children affected by dyslexia as well as when dyslexics are compared to either an age-matched or reading-matched control group. The deficiencies in the left temporo-parietal and occipito-temporal regions in dyslexia furthermore have been uncovered across different languages. Krnobichler et al. (2006) in fact found underactivation of the left occipito-temporal cortex and left supramarginal gyrus as well as an overactivation of the inferior frontal region in German dyslexics. Paulesu et al. (2001) on the other hand found underactivation in the left middle inferior and superior temporal cortex and in the middle occipital gyrus across samples of Italian, English, and French dyslexic participants. The authors thus suggest that a phonological processing deficit is universally present in dyslexia and is present in both shallow and deep orthographies.

In conclusion, functional imaging studies on dyslexia clearly indicate differences in brain activations between dyslexics and nonimpaired readers during reading tasks. Abnormally low activations in the temporo-parietal and occipital-parietal regions as well as hyperactivation of frontal regions are among the most common findings when reviewing the literature on functional imaging studies on dyslexia. The majority of these investigations are based on a comparison between dyslexic readers and non-impaired readers, either matched by age or by reading abilities, or a comparison between different groups of dyslexics, with common interpretations associating the temporo-parietal region to phonological processing, the occipito-temporal area to orthography, and frontal overactivation to compensatory mechanisms. Despite some consistencies between studies, however, there is still a great deal of variability regarding the areas of activation and the interpretation of results.

b. Structural imaging studies on dyslexia

In addition to functional imaging investigations on dyslexia, there are several structural studies that have been conducted to identify abnormalities in the morphology and structure of the brain of individuals with dyslexia. Structural investigations on dyslexia include post-mortem and histological studies as well as experiements using voxel-based morphometry (VBM), diffusion tensor MRI (DTI), or volumetric analysis.

The post-mortem investigations by Galaburda and colleagues were among the first studies highlighting structural abnormalities in dyslexia and leading to the foundation of further research on dyslexia. Their study of 100 brains of individuals with dyslexia revealed asymmetry anomalies of the planum temporale, cortical scars, dyslamination and ectopias (Galaburda et al., 1985). Other post-mortem and histological studies on dyslexia has overall highlighted different anomalies, including neuronal abnormalities in the auditory cortex (Galaburda & Kemper 1979), perisylvian cortex (Galaburda et al., 1985), lateral (Livingstone et al., 1991) and geniculate nuclei medial (Galaburda et al.,

1994) primary visual cortex (Jenner et al., 1999) and cerebellum (Finch et al., 2002).

The advances in the field of neuroimaging allowed further investigations on the brain structure and morphology of those affected by dyslexia. Overall, structural imaging on this disorder pinpoint to relatively consistent findings for abnormalities in the temporo-parietal cortex, inferior temporal gyrus, corpus callosum, and cerebellum (Eckert et al., 2004).

Several Voxel-based Morphology (VBM) studies on dyslexia has yielded to anomalies in the temporal gyri and in the occipital-temporal cortex. Vinckenbosch et al. (2005), for instance, used VBM to find reduced gray matter density in the middle and inferior temporal gyri, increased grey matter density in the bilateral precentral gyri, as well as a positive correlation between grey matter denisity in these regions and performance on a rhyme judgement task. Brambati and colleagues (2004) also used VBM and found similar reductions of grey matter volume as well as Silani and colleagues, who showed morphological abnormalities of gray and white matter densities in the same regions across 3 different groups of nationalities (Italians, French, and English dyslexics), thus sustaining the view of a universal neurological basis for dyslexia in these regions. Kronbichler et al. (2006) confirmed grey matter abnormalities in the left occipito-temporal cortex in dyslexic Germans, with the cerebellum showing the most prominent difference in grey matter volume. Finally, the VBM study by Hoeft et al. (2007) yielded to reduction in gray matter volume in the left parieto-temporal region as well.

Aside from grey matter anomalies in dyslexia, a number of other studies were able to detect abnormalities in white matter tracts as well. Several diffusion tensor imaging (DTI) studies on dyslexia found left temproro-parietal white matter deficits, both in terms of reduced anisotropy and anomalies in the corpus callosum (Klingber et al., 2000; Deutsch et al., 2005; Kingber et al., 2000; Beaulieu et al., 2005; Niogi & McCandliss, 2006; Dougherty, 2007; Von Plessen et al., 2002). Volumetric analyses have also found alterations in the brains of those affected by dyslexia, including anomalies in the cerebellum (Rae et al., 1998, 2002; Kibby et al., 2008).

In conclusion, structural imaging studies on dyslexia provide evidence and some consistency regarding dysfunctions in different areas of the brain of individuals with dyslexics, with common findings including structural grey and white matter anomalies in the temporo-parietal, cerebellum, and corpus callosum in dyslexia.

c. Limitations and inconsistencies in neuroimaging studies on dyslexia

As one may infer from the above review, neuroimaging has been an extremely useful tool in studying and examining the brain of individuals affected by dyslexia and reading impairments. Nevertheless, the literature on neuroimaging investigations on dyslexia also discloses limitations and inconsistencies in findings and interpretation of findings. As reading relies on a widespread distribution of neural circuits, the structural and functional discrepancies can be partly attributed to the heterogeneity of reading networks and of DD in terms of its cognitive and neural profiles as well as to other aspects described below. The following paragraphs in fact, succinctly describe the difficulties and inconsistencies between studies encountered during functional and structural research on DD respectively.

Functional imaging enables us to study the brain areas that are recruited for reading and the deficient patterns associated with dyslexia. To gather the information regarding brain regions involved in reading, participants are required to engage in a reading task during scanning. Although there has been some consistency in showing underactivation in left temporo-parietal, occipito-temporal, and cerebellar regions, there is also a great deal of inconsistencies and none of the results survive an unbiased correction for multiple comparisons across the whole brain (Kherif et al. 2008). Heterogeneity of reading networks and DD, inter-subject variability, differences in stimulus presentation, discrepancies in performance between dyslexics and controls, and difficulties in interpreting results account for some of the inconsistencies in functional imaging.

It has been noted that due to the heterogeneity of dyslexia and of reading networks, even within the same sample of readers there may be differential brain activations when subjects are performing the same language task. Inter-subject variability may then interfere with results and the variation may be interpreted as error variance rather than meaningful variance; this aspects also ties in the fact that functional imaging, as a quite sensitive tool for detecting change, may furthermore pick up on irrelevant noise (Kherif et al. 2008). The use of different tasks to assess abnormalities in brain activations during reading also is a source for inconsistencies of findings. As explained by Hoeft et al. (2006), poorer reading abilities or in-scanner performance may be accounting for the differences in activation levels between dyslexics and non-impaired readers. Finally, interpretation of results is also a great source of debate; functional data in fact is difficult to interpret as results can be attributed to the disorder per se' as much as to differences in stimuli, performance levels or compensatory mechanisms. Controlling for stimulus presentation, performance levels of correct trials, as well as combining data from different sources of investigation may allow us to partly overcome some of the inconsistencies in results and the limitations of functional studies on dyslexia.

Compared to functional imaging, structural imaging has the advantage of not requiring the subject to engage in any cognitive task. Results and differences between groups thus may be relatively more easily interpreted in terms of the neural basis underlying dyslexia. Nevertheless, it is still difficult to infer whether the differences and abnormalities are a cause or a consequence of the disorder. Moreover, recent evidence sustains structural brain alterations with experience (May et al., 2007), which may then interfere with the interpretations regarding structural differences between dyslexics and controls. Structural imaging research on dyslexia is then also intertwined with difficulties in interpretation of results.

In conclusion, what is important to understand is that there is significant variability in structural and functional results of studies on DD. As a whole, some of the reasons for inconsistencies in neuroimaging may lie in the variability of impairments in dyslexia and widespread distribution of reading-related brain sites (Silani et al., 2005), inter-subject variability, as well as the use of different techniques across studies (including stimuli presentation and performance levels). Other possible explanations for discrepancies in results are attributable to the different inclusion criteria that studies have used to select their participants. The studies that have been reviewed examined samples of dyslexics that presented with wide ranges of reading impairments, which in turn may lead or explain some of the weak or inconsistent effects found (E.g. Eckert et al., 2004; Kibby et al., 2007; Phinney, 2007; Zadina, 2006). In light of the wide range of deficits in DD and inconsistencies of neuroimaging findings, questions across the literature arise concerning the existence of subtypes of dyslexia, in turn explaining the variability of results between studies. The hope is that more consistency in findings may be achieved if focusing on samples of subtypes of dyslexics with more homogenous profiles.

3) Summary of studies on sub-grouping dyslexics:

The heterogeneity of dyslexia might partly be responsible for the inconsistencies in neuroimaging findings. Therefore, several attempts to confirm whether there are different subtypes of dyslexia associated with distinct profiles may allow comparisons between more homogenous subgroups of dyslexics to non-impaired readers. A strong debate however still pervades the literature concerning the existence or not of different subtypes of dyslexia and an even greater controversy exists regarding what those subtypes might be and how to classify dyslexic readers. The final goal of categorizing dyslexics and study their neural and behavioural trails is fundamental as it relates to the possibility of designing then more efficient interventions to better meet the needs of the subgroups of individuals. The following paragraphs aim to describe the empirical efforts, started around the 1970s, that have been made in an attempt to confirm the existence of subgroups of DD.

A classic categorization of dyslexia was proposed by Castle & Coltheart (1993), whom classified dyslexia in two subgroups: surface and phonological dyslexia. The majority of their sample of dyslexics showed a phonological deficit (55%), characterized by a greater impairment for nonword reading than for irregular words.

Surface dyslexics accounted for 30% of the total sample and showed the reversed pattern, specifically a greater impairment for irregular word reading than for nonword reading. The authors concluded by supporting the view of dyslexia as a non homogeneous disability and claiming that their results support the existence of distinct subtypes of DD and the notion of a clear dissociation between reading patterns.

While results from Murphy and Pollatsek (1994) however were not in agreement with the differentiation of phonological and surface dyslexia, other experiments have been conducted and confirmed the existence of possible variants of dyslexia. The results of Castle & Coltheart (1993) supporting the existence of a phonological and surface distinction of dyslexia were in fact also replicated by Manis et al. (1994), Wolf et al. (1994), and Stanovich et al. (1997). Stanovich and colleagues (1997) referred to one group as having a "specific" reading disability with a core deficit in phonological processing and to the other subgroup as the "garden-veriety" poor readers with a wider spectrum of language impairment. Wolf et al. (1994) also reached similar conclusion when the research team identified distinct subgroups of children with reading disability: those characterized by a phonological deficit, those identifiable for their impairment in rapid naming, or those characterized by both deficiencies. In 2004, Lachmann and colleagues also pinpointed to the existence of two subgroups of dyslexics, with one group demonstrating greater impairments in non-word reading, whereas the other one showing mostly word-reading deficits.

Other empirical studies attempting to demonstrate the existence of subtypes of dyslexia have used novel approaches to classify subgroups of dyslexics. Morris et al. (1998), for instance, relied on several tasks assessing cognitive and language functions in children with dyslexia and cluster analysis to identify hypothetical subtypes of this disorder. Seven subtypes were revealed by cluster analysis; two subgroups were globally deficient in language skills, four presented prominent deficits in phonological awareness and in rapid naming and verbal short-term memory, whereas one group showed impairments on verbal and nonverbal tasks in terms of rate and accuracy scores.

Cluster analysis was also used by Heim et al. (2008) to identify congnitive subgroups of dyslexics. Three subgroups of dyslexics characterized by different cognitive deficits were identified: group 1 was characterized by poor phonological awareness; group 2 by poor phonological awareness, auditory discrimination, and magnocellular dysfunctions; whereas group 3 demonstrated the most prominent deficit in attentional reorienting. King et al. (2007) on the other hand, confirmed the existence of different types of dyslexic phenotypes using resampling and gap statistics. Four clusters were identified, with 80% of the dyslexic subjects belonging to one of the first three clusters: a phonological deficit cluster, a rapid-naming cluster, a cluster characterized by both deficits and the fourth cluster showing neither deficit.

While some experiments identified different subgroups of dyslexics on the basis of behavioural impairments (e.g. Castle & Coltheart, 1993), other studies have compared subgroups of dyslexics based on other factors. Shaywitz et al. (2003), for instance, subgrouped dyslexics into compensated versus persistently poor dyslexic readers. The study found a divergence in brain activation patterns between the two subgroups of dyslexics; based on the differences in brain activation, risk factors, and compensatory resources between the subgroups, the authors sustained two possible types of reading disability: a genetic type with higher IQ scores and an environmental influenced type with lower IQ scores.

As shown, the literature on subgrouping dyslexic readers is quite extended and results vary significantly in terms of numbers of subgroups found and their characteristic impairments. The variability in findings reflects differences between studies in terms of definitions, goals, methods and tasks, as well as conclusions of investigations focused on classifying dyslexics. The debate on the categorization of dyslexics is therefore an on ongoing issue as well as the exploration of reliable methods to identify subtypes of dyslexia.

In conclusion, the present introduction, consisting of a general overview of dyslexia, a review of neuroimaging research, and a description of subgrouping techniques and findings, aspired to introduce the reader to the background that has prompted the present research project. In particular, the review of functional, structural and subgrouping studies aimed to show a) the approach of studying dyslexia (either through comparison between dyslexics and non-impaired readers or between subgroups of dyslexics based on behavioural traits), b) the inconsistencies in findings and the possibility that methodological issues as well as the heterogeneity of dyslexia might play a role in this matter, and c) the dispute regarding the existence of subgroups of dyslexia and what those subtypes may be.

Due to the heterogeneity of DD, inconsistencies, and the debate regarding subtypes of dyslexia, the current fMRI study used a novel and unbiased approach to identify subgroups of dyslexics to consent the identification of more homogenous samples of dyslexics to study. The goal was to identify subgroups of dyslexics based on brain activations during reading aloud familiar words, and then to determine any neural and behavioural differences between the subgroups.

Once functional and behavioural data were collected, the study involved running a one sample t-test, applying Principle Component Analysis (PCA) and Gaussian Mixture Modelling (GMM) and running statistical analyses to identify subgroups of dyslexics and define the differences in brain activation and behaviour between them. The PCA/GMM procedure is a novel clustering approach that does not rely on *a priori* knowledge of the subgroups. Subjects assigned to the subgroups were hypothesized to display similarities in brain activations to members of their subgroup but differences compared to those belonging to other subgroups.

II. METHODS

1) Aim

The present fMRI study aimed to 1) identify subgroups of dyslexics based on brain activation while reading familiar words, using Principle Component Analysis (PCA) and Gaussian Mixture Modelling (GMM); 2) establish neural differences that characterize the subgroups using conventional ANOVA; and 3) investigate behavioural differences that distinguish and describe each subgroup using Mann-Whitney U statistical analysis. My role within the present research project included behavioural assessments of the subjects recruited in 2008 and behavioural data analysis.

2) Participants

The study involved a total of 68 right-handed subjects, 34 dyslexic readers (20 males, 14 females, aged 16-28 years, and mean age 20 years) and 34 non-impaired readers (19 males, 15 females, aged 16-51 years, and mean age 20.8 years). Functional and behavioural data from twenty subjects had been collected in 2004 for another study on dyslexia, while the rest of the participants were recruited in January 2008. Recruitment of subjects occurred through a number of sources, including referrals from psychologists, dyslexic organizations, university services, and ads; the diagnosis of dyslexia on the other hand had been determined by education psychologists' reports prior to subjects' enrolment in our study. Inclusion criteria included right-handed and MRI compatible (i.e. no braces and aged 13 years old and over) subjects, with no neurological, psychiatric diseases, or attention deficit disorders, and already in possess of an assessment of dyslexia before enrolment.

Informed consent was then obtained from each subject prior to the initiation of the investigation. A demographic description of the subjects participating in the study can be found in Table 1. There were no differences in gender, age, or IQ scores between the control group and the dyslexic sample.

	NON-IMPAIRED SUBJECTS	DYSLEXIC SUBJECTS
# SUBJECTS	34	34
AGE	20.8 *(7)*	20 *(3)*
GENDER	1.4 *(1)*	1.4 *(0)*
WAIS III		
VIQ	122 *(16)*	107 *(13)*
PIQ	112 *(10)*	109 *(13)*
FSIQ	120 *(14)*	108 *(11)*

TABLE 1. Group demographics. Values presented are means and standard deviations (SD) (for non-impaired and dyslexic subjects) for age, gender, and for the Wechsler Adult Intelligence Scale III (WAIS III), which includes verbal IQ (VIQ), performance IQ (PIQ), and full scale IQ (FSIQ).

3) Design and Procedures

Participants were administered a series of psychometric tests, assessing IQ levels as well as reading and other abilities. One structural and four functional brain images were then obtained from each subject while they engaged in a task involving reading real words. The experiment lasted approximately 6 hours for both the behavioural assessment and scanning of each subject, all of whom were compensated in monetary terms (60 pounds) at the end of their participation. The next paragraphs illustrate a detailed description of the a) behavioural assessment and b) functional imaging procedures followed in this study for data collection.

a. Behavioural assessment

Intelligence quotient (IQ) measurements were obtained using the Wechsler Adult Intelligence Scale III (WAIS), which calculates verbal and non-verbal IQ scores (appendix 2 on page 55 reports the subtests constituting the WAIS III). Reading accuracy and reaction times were assessed using the Wide Range Achievement Test (WRAT), Wechsler Test of Adult Reading (WTAR), and the National Reading Test (NART). The behavioural assessment also examined word and nonword spelling abilities (using the WRAT), phonological skills (using the Phonological Assessment Batter, *PhAB*; spoonerism and nonword repetition tasks), and auditory perception skills (using the Psycholinguistic Assessment of Linguistic Processing in Aphasia, *PALPA*). A list of the behavioural tests with a description of the skills they are aimed to assess can be found in the appendix on page 555 (Appendix 1 and 2).

b. Functional imaging

In the current fMRI study, one structural and four functional images for each subject were collected using a 1.5T MRI scanner (Siemens Medical Systems). The structural image was obtained to assure that the subjects were neurologically normal, while functional images of the brain were acquired as subjects read familial words. Each participant was trained and given instructions prior to scanning, while also reminded about minimizing head and lip movements during the brain image acquisitions.

Stimuli: The activation task during scanning involved reading aloud 96 high frequency words made of 3-7 letters with regular spelling to sound relationships (e.g. "cat", "ship"). The study included also other paradigms, namely articulatory and visual tasks (picture naming and saying "1,2,3" in response to meaningless symbols or non-objects) to separate brain activations specific for reading from those recruited for articulation and visual processing. A video projector, panel and a system of mirror fastened to a head coil, helped present items centrally on the screen inside the scanner. Participants were fully instructed outside and inside the scanner, to read words on the screen clockwise, starting from the top, while making as little lip and head movements as possible. In order to detect the areas of activation for reading familiar words relative to rest, a baseline /fixation condition was also employed. A total of sixteen blocks of reading, eight blocks of picture naming, eight blocks of saying "1,2,3" to meaningless items, and twelve bocks of fixation were presented to the subjects, the order of which was fully counterbalanced. Traids of blocks lasted 18 seconds with 12 stimuli per block. Words were in lower case Arial font, with a maximum visual angle on the retina of 4.9° x 1.2°.

c. Data analysis

Functional imaging analysis: Because of frequent movement artefacts, images from each run were motion corrected. Criteria for rejection were motion exceeding 1.5 mm translation. Data analysis was performed using SPM5 (Statistical Parametric Mapping), which allowed for spatial transformation, temporal pre-processing transformation to remove noise and signal drift, and statistical analysis.

Functional imaging analysis included several stages: 1) running a one sample t-test to compare images for reading aloud to fixation, to sum over functional images from subjects, to identify reading activation at multiple levels, and to treat inter-subject variability as error variance; 2) applying PCA to treat error variance; 3) utilizing GMM to identify subgroups of dyslexics and categorize subjects to the subgroups; and finally 4) running a conventional ANOVA to examine regional differences between the subgroups in terms of brain activations when reading aloud. In other words, ANOVA was used to establish the existence of any specific neural profiles that distinguished the subgroups on a voxel by voxel basis.

PCA, a statistical approach used for dimension reduction in a data set, was used and applied to the inter-subject variability to identify the main source of variance. The GMM is a simple hierarchical Bayesian technique that has already been reported and validated as a cluster classification and assignment tool by Noppeney et al. (2006) and Kherif et al. (2008). In the present study, it allowed us to recognize a precise number of subgroups among the sample of dyslexics and then to assign the subjects to each of those groups. Following subjects' assignment to subgroups, it was hypothesized that the subjects in one subgroup would display similarities in activation patterns between each other, but dissimilarities compared to subjects in other subgroups.

The novelty of this approach relies on the fact that the PCA/GMM procedure is an unbiased approach, as it does not depend on *a priori* knowledge to identify subgroups of dyslexics. As highlighted in the introduction, the majority of studies on subgrouping dyslexics have relied on a subdivision in terms of behavioural performance (surface versus phonological dyslexics or persistent versus compensated dyslexics for example) or of other previously established criteria, such as socioeconomic status. Figure 2 reproduces an archetype of the PCA/GMM analysis approach used in this study.

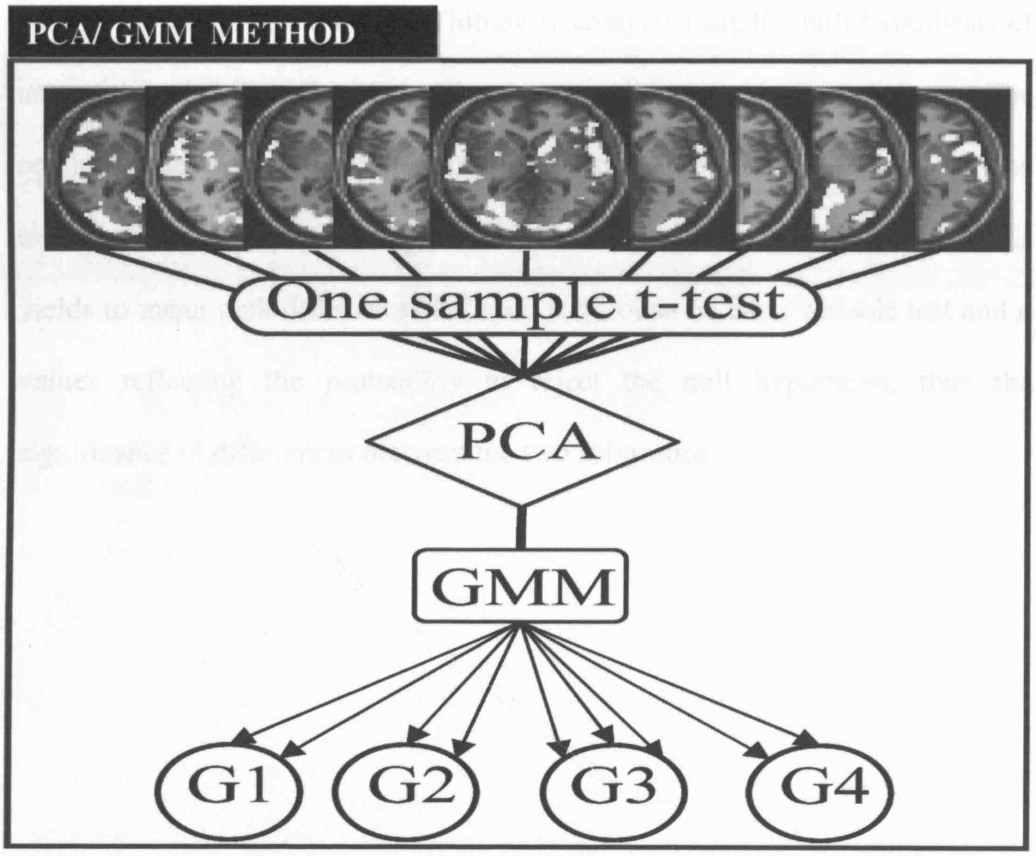

Figure 2. Functional imaging analysis involving running a one sample t-test, Principal Component Analysis (PCA) and Gaussian Mixture Modelling (GMM) to identify subgroups and assign subjects to the subgroups

<u>Behavioural analysis:</u> Once the subgroups and their activation differences had been identified, the study investigated any behavioural differences between the subgroups. Behavioural data was analyzed using SPSS 14.0 (Statistical Package for Social Sciences) for Windows. Because the distribution of the behavioural data was not normal, conventional ANOVA to compare the

behavioural performance on the psychometric tests between the subgroups could not be used. Instead, to assess whether the different subgroups displayed different phenotypes or behavioural profiles we used a non-parametric test, specifically the Mann-Whitney U statistical test. As a well established non-parametric analysis, the Mann-Whitney U analysis tests the null hypothesis of an equal probability distribution between two independent populations. The results of the analysis aim to estimate the probability that performance on one task in one subgroup exceeds performance in a second subgroup. The analysis yields to mean rank differences between subgroups on each variable test and *p* values reflecting the probability to reject the null hypothesis, thus the significance of differences between the two subgroups.

III. RESULTS

Identification of subgroups of dyslexics: A one sample t-test analysis revealed brain activations for correct responses during reading relative to fixation for each subject. The PCA was then applied to the treat the inter-subject variability and the GMM identified as well as assigned subjects to the subgroups. The GMM identified three subgroups of dyslexics based brain activation for reading tasks (D1, D2, and D3), comprising respectively of 16, 2, and 16 subjects with dyslexia.

Functional results: Once identified the 3 subgroups of dyslexics, we ran a conventional ANOVA to investigate differences in brain activation at a voxel level characterizing each subgroup during reading. Correction (p value < 0.05) for multiple comparisons across the whole brain yielded to significant differences in brain activations between between the subgroups. Compared to controls and other subgroups, D1 over-activated bilaterally the superior temporal gyri (STG) (x= -56, y= -14, z= 2; and x= 60, y= -16, z= -10) ($p < 0.05$). Compared to controls and D1, both D2 and D3 subjects showed statistically significant reductions in activation levels in three areas, namely in the bilateral temporo-parietal cortex, left occipito-temporal cortex, and cerebellum. Comparisons between D2 and D3 revealed on the other hand differences in the medial occipital cortex ($p<0.05$ corrected for the whole brain), with subjects in D2 presenting deactivation in this area (x= 4, y= -72, z= -4; x= -2, y= -76, z= 30; and x= 20, y= -72, z= 20) and with subjects in D3 showing over-activation.

In conclusion, our results showed abnormalities in activation patterns that varied according to the dyslexic group. Thus, the *a priori* hypothesis regarding differences in brain activation between subgroups of dyslexics was confirmed by our results. In other words, different brain activation patterns distinguished the three groups.

SUBGROUP	UNDERACTIVATIONS	OVERACTIVATIONS
D1 (versus controls, D2 & D3)	*Nothing significant*	Bilateral STG
D2 & D3 (versus controls & D1)	Bilateral T-P Cerebellum Left OT	*Nothing significant*

TABLE 2. Brain regions showing abnormal activations (underactivation or overactivation) between dyslexic subgroups when compared to controls and to each other; (p value < 0.05; corrected for entire brain or in left occipito-temporal at 48, -56, -16). D1, D2, D3= dyslexic subgroup 1, 2, and 3; STG= superior temporal gyrus; T-P= temporo-parietal cortex; OT= occipito-temporal cortex.

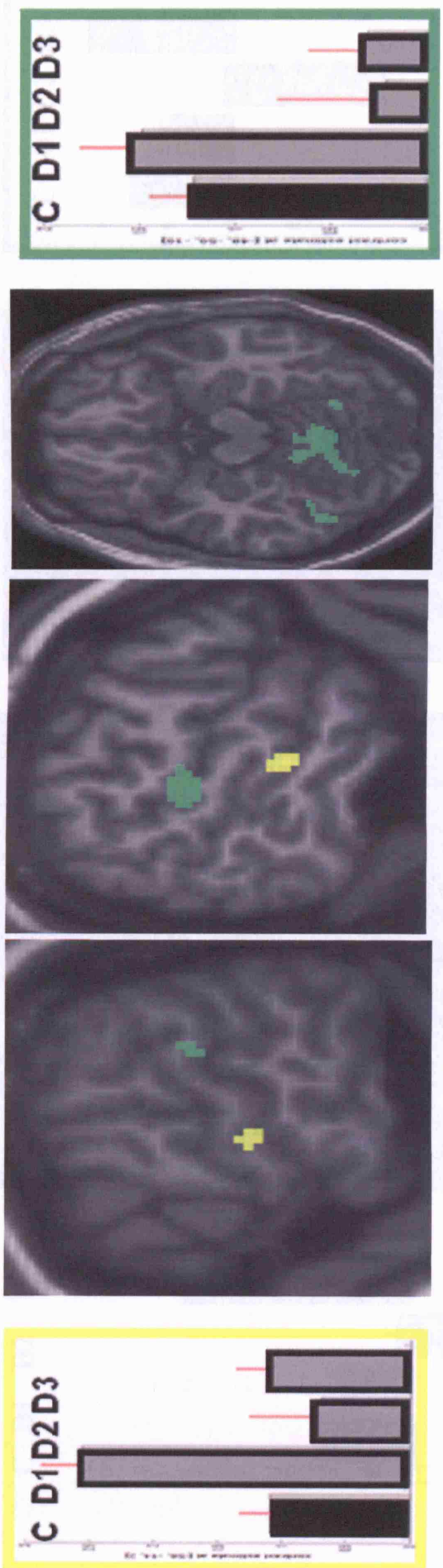

Figure 3. Brain regions of over-activation and under-activations for the three subgroups of dyslexics. Yellow: over-activation for D1; Green: underactivation for D2 and D3

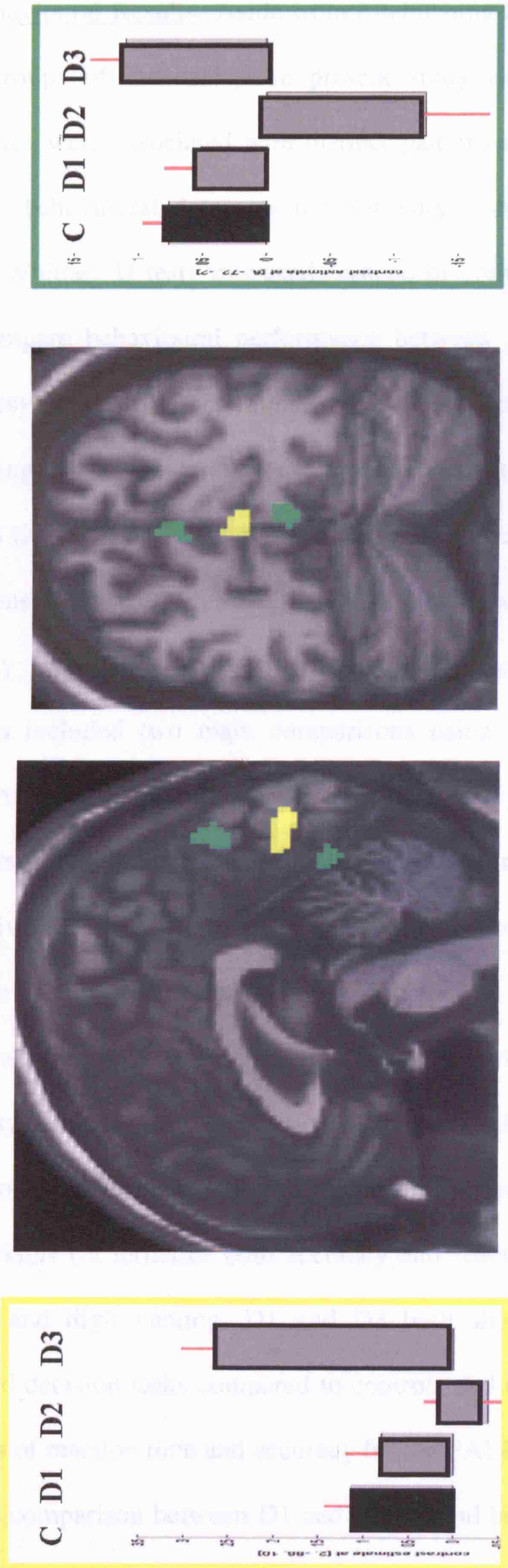

Figure 4. Differences in activation patterns between D2 and D3 in the middle occipital cortex ($p < 0.05$, corrected for the entire brain). Yellow: overactivation for D3; Green: underactivation for D2

<u>Behavioural Results</u>: Aside from establishing neural differences between the 3 subgroups of dyslexics, the present study assessed whether the different subgroups were associated with distinct patterns of behaviour. Due to the fact that the behavioural data was not normally distributed, a non-parametric test (Mann-Whitney U test) was used, instead of conventional ANOVA, to analyse and compare behavioural performance between 2 subgroups (D1 and D3) on every psychometric test administered to the subjects. The reason why subjects belonging to the D2 group were not included in the analysis and comparison reflects the fact that D2 comprised only two subjects with full behavioural data, thus constituting an excessively small sample size to analyse appropriately and possibly representing outliers within the dyslexic sample. The behavioural analysis included two main comparisons using the Mann-Whitney U test: a comparison between dyslexic versus control groups and a comparison between D1 versus D3 subjects, in an attempt to delineate behavioural differences respectively between the dyslexics relative to controls and, more importantly, between D1 and D3 subjects.

Compared to controls, dyslexics (both D1 and D3) showed impairments on most psychometric tests. Specifically, dyslexics showed deficits in performance in the following tests: spelling words (accuracy), word and nonword reading and spoonerisms (in terms of both accuracy and reaction times), reaction times for picture and digit naming; D1 and D3 both showed also worse accuracy in nonword decision tasks compared to controls and commonly showed difficulties in terms of reaction time and accuracy for the PALPA nonword test.

The comparison between D1 and D3, to find behavioural traits defining each subgroup, also yielded differences. In terms of age, gender, and performance IQ, the two subgroups of dyslexics showed no statistically significant differences, aside from a possible tendency for worse performance in arithmetic in D1 subjects compared to D3, which did not reach significance ($p = 0.07$). However, the Mann-Whitney U test did show statistically significant differences in accuracy during non-word repetition ($p = 0.03$) (table 5), with D3 subjects performing worse relative to D1 subjects. The behavioural analysis also found a tendency for a possible difference between the subgroups in word spelling ($p = 0.06$) and lexical decision nonword tasks, however the difference did not reach significance.

In order to assess whether the non-significant results could have been driven by outliers in the subgroups, we plotted the distribution for each group on different tasks. A few outliers were revealed when plotting the distribution, but results did not change when these were omitted from the analysis. It is of importance also to mention that, although the Mann-Whitney U test highlighted a significant difference between D1 and D3 only in non-word repetition tasks, performance means (see table 5) show that subjects in the D3 subgroup tended to perform overall worse on most tests, except on arithmetic.

In conclusion, few statistically significant differences were highlighted following a non-parametric behavioural analysis using Mann-Whitney U tests to compare D1 and D3 on every psychometric test administered to the subjects. The analysis showed significantly worse performance on the part of subjects in the D3 subgroup during non-word repetition tests tapping into auditory short term memory skills. D3 subjects also showed a tendency, not reaching significance however, for lower performance in word spelling and lexical non-word decision tasks.

	CONTROLS	D1	D3	D1 vs. D3
# SUBJECTS	34	16	16	
AGE	20.8	20.1	20.2	ns *(p =0.76)*
GENDER	1.4	1.5	1.4	ns *(p=0.48)*
PIQ	112	109	109	ns *(p=0.81)*

TABLE 3. Description of the number of subjects in each group (controls, D1, and D3) and means calculated for age, gender and performance IQ for control subjects, dyslexics belonging to the subgroup D1 and those belonging to D3. There were no statistically significant difference between dyslexics and controls and between subgroups of dyslexics in terms of age, gender and performance IQ. ns= non-significant difference between D1 and D3, with *p values* written within parenthesis.

TESTS		CONTROL	D1	D3	D1 versus D3
Word Reading (WRAT)	*Accuracy*	36 *(4)*	33 *(4)*	32 *(5)*	ns *(p=0.9)*
	RT	1.4s	1.8s	1.9s	ns *(p=0.67)*
Nonword Reading	*Accuracy*	19 *(2)*	17 *(3)*	17 *(2)*	ns *(p=0.89)*
	RT	1.5s	2.2s	2.3s	ns *(p=0.67)*
Boston naming	*Accuracy*	28 *(2)*	26 *(1)*	26 *(3)*	ns *(p=0.96)*
Rapid picture naming (PHAB)	*Accuracy*	50 *(1)*	50 *(1)*	50 *(1)*	ns *(p=0.63)*
	RT	31s	37s	36s	ns *(p=0.48)*

Rapid digit naming (PHAB)	*Accuracy*	50 *(0)*	50 *(0)*	50 *(1)*	ns *(p=0.63)*
	RT	18s	22s	24s	ns *(p=0.50)*
Spoonerisms	*Accuracy*	10 *(2)*	8 *(2)*	8 *(3)*	ns *(p=0.64)*
	RT	6s	10s	11s	ns *(p=0.70)*
PALPA (non-words)	*Accuracy*	36 *(1)*	33 *(5)*	35 *(1)*	ns *(p=0.58)*
	RT	0.63s	1.8s	0.64s	ns *(p=0.17)*
PALPA (words)	*Accuracy*	35 *(1)*	33 *(4)*	34 *(1)*	ns *(p=0.28)*
	RT	0.74s	1.5s	0.71s	ns *(p=0.11)*
PALPA (rhyme)	*Accuracy*	31 *(4)*	25 *(5)*	28 *(4)*	ns *(p=0.17)*
	RT	4.02s	3.73s	3.9s	ns *(p=0.56)*
Non-word repetition	*Accuracy*	36 *(3)*	37 *(3)*	34 *(4)*	D3 Worse *(p=0.03)*
	RT	2.4s	2.5s	2.7s	ns *(p=0.66)*
Word Spelling (WRAT)	*Accuracy*	32 *(4)*	26 *(4)*	23 *(5)*	Weak significance D3 Worse *(p=0.06)*

Nonword Spelling (WRAT)	*Accuracy*	16 *(3)*	15 *(4)*	13 *(5)*	ns *(p=0.48)*
Lexical decision (nonwords)	*Accuracy*	18 *(2)*	15 *(2)*	14 *(3)*	ns *(p=0.18)*
	RT	1.19s	1.3s	1.6s	ns *(p=0.67)*
Lexical decision (words)	*Accuracy*	18 *(1)*	17 *(1)*	14 *(2)*	Weak sig. D3 worse *(p=0.08)*
	RT	0.8s	1.14s	1.11s	ns *(p=0.48)*

TABLE 4. Means *(and standard deviations, SD)* scores for controls, D1 subjects, and D3 subjects on each psychometric test. The last column depicts whether there was significant difference (*p values*) in behavioural performance when comparing D1 and D3 using Mann-Whitney U test to analyse the data; differences in performances were considered significant at *p* value < 0.05). RT= reaction times; ns= non significant differences

Ranks

	Subgroup numeric	N	Mean Rank	Sum of Ranks
nonword_rep_total	1.00	15	19.63	294.50
	2.00	16	12.59	201.50
	Total	31		

Test Statistics [b]

	nonword_rep_total
Mann-Whitney U	65.500
Wilcoxon W	201.500
Z	-2.165
Asymp. Sig. (2-tailed)	.030
Exact Sig. [2*(1-tailed Sig.)]	.030[a]

a. Not corrected for ties.

b. Grouping Variable: Subgroup numeric

TABLE 5. Comparison using Mann-Whitney U test between D1 and D3 on performance in nonword repetition task. The results show a significant difference between the two subgroups, with D3 subjects performing worse in this task (p = 0.03)

IV. DISCUSSION

The inconsistencies in the results of cognitive, structural and functional imaging studies on dyslexia have sparked an important debate regarding the existence or not of different subtypes of dyslexia accounting for the discrepancies. Several experiments have thus attempted to unravel and categorize individuals with dyslexia into more homogeneous subgroups. Identifying subgroups would allow more homogeneous samples of dyslexics to be studied with the hope of detecting neuronal markers of dyslexia. The final hope is to be able to shape remediation strategies to the specific needs of the type of dyslexia a person is affected by for a better and more efficient management of deficits.

In light of the inconsistencies of results on dyslexia, the heterogeneity of dyslexia and the noteworthy issue of subcategorizing dyslexia, the present fMRI study aimed to identify subtypes in a sample of 34 dyslexics using an unbiased classification method (PCA/GMM). Having identified three subgroups of dyslexics (D1, D2, and D3) based on brain activations using fMRI during real-word reading, we investigated the neural and behavioural traits distinguishing them. Regional activation differences for the subgroups were identified across the whole brain by comparing each subgroup to all others ($p<0.05$ after family wise correction for multiple comparisons), while conventional ANOVA and the Mann-Whitney test assessed neural and behavioural differences between subgroups.

Overall, our results are consistent with other functional imaging studies highlighting abnormally low activation patterns in posterior neural systems in the parieto-temporal and occipiol-temporal regions. Aside from the abnormal activation differences between the dyslexic group as a whole compared to non-impaired readers during reading, this study was furthermore able to show that brain activation patterns and behaviour diverged within the sample of dyslexics as well, i.e. subgroups of dyslexics differed from each other in terms of brain activations and behaviour for the same tasks. Succintly, D1 (N= 16) showed overactivation of the STG. D3 (N=16) on the other hand showed underactivation in three posterior brain regions (temporo-parietal, occipito-temporal and cerebellum). The following discussion will examine the areas of abnormal underactivation and overactivation characterizing the subgroups of dyslexics in our study (temporo-parietal, occipito-temporal, STG and cerebellum respectively) and their role in DD. Aside from the neuroimaging findings, the discussion will also focus on the behavioural results and on the combination of neural and behavioural data, as well as the limitation, difficulties and implications of the present project, and future directions for research on dyslexia.

According to Logan (1988, 1997), two systems are critical for skilled and successful reading. One system is considered to be necessary for analyzing the written word, involving an analysis of single units and attention resources while processing words relatively slowly. Word analysis has been hypothesized and supported to be localized within the temporo-parietal posterior brain area. Dejerine in 1891, had already back then suggested the involvement of this posterior brain region in reading and since then, a large body of literature has supported the view of the involvement of the temporo-parietal area in analyzing words. In our study, this area has been shown dysfunctional (significantly more underactivated) among D3 subjects compared to D1 dyslexics and controls.

A second system important for reading proposed by Logan (1988, 1997), and Dejerine in 1982, is the one that operates on the whole word (word form), does not require attention and processes rapidly. The occipito-temporal area is thought to play a critical role for automatic, whole-word recognition reading approach. This region has been shown to increase in activation as reading skills improves (Shaywitz et al., 2002) and to respond to rapidly presented, and not necessarily consciously perceived, stimuli (Price et al., 1996; Salmelin et al., 1996; Dehaene et al., 2001). Again dysfunctions in the occipito-temporal region had also been found in our study, although only in subjects belonging to the D3 subgroup, and not among those in the D1 group.

Overall, several other studies on dyslexia have found structural and functional dysfunctions or anomalies in these very regions (Brambati et al., 2006; Brunswick et al., 1999; Hoeft et al., 2006; Hoeft et al., 2007; McCroy et al., 2004; Meyler et al., 2007; Rumsey et al., 1997, 1998, 1999; Shawitz et al., 2002; Shaywitz et al., 2003; Shaywitz et al., 2007). The neural deficits in temporo-parietal and occipito-temporal regions have furthermore been demonstrated in different languages (Silani et al., 2005; Deutsch et al., 2005). Referring to the dyslexic group as a whole, the present investigation is then consistent with these studies, as it has highlighted underactivations in temporo-parietal and occipito-temporal regions. The underactivations however were found only among D3 subjects (D2 as well, but not discussed as the group was made of only 2 subjects), and not among D1 subjects. The findings then support the involvement of the temporo-parietal and occipito-temporal areas in dyslexia, but not for all affected subjects. It may well be that these deficits characterize the neural circuits of only one specific subtype of dyslexia. Despite the greater abnormalities and reductions in brain activations in the D3 subgroup compared to D1, however, the two subgroups did not show major statistically significant differences in performance during tests assessing accuracy and reaction times for reading words and nonwords as one would expect from brain activation differences.

Aside from the temporo-parietal and occipito-temporal areas, another common neuroimaging finding in dyslexia research includes activations of an anterior system, specifically the inferior frontal gyrus, often associated with articulation and compensatory mechanisms (Shaywitz et al., 2002). While some studies of dyslexics have found increased activation in frontal regions in dyslexia, others have found a reduced pattern of activation (Shaywitz et al., 2002). In the present study, we did not find hyperactivation in frontal regions. However, D1 did show increased brain activation in the superior temporal gyrus (STG) compared to both controls and D3; D3 on the other hand showed no areas of over-activity.

The STG has received relevant support for playing an important role in phonological coding and processing (Henderson, 1986; Rumsey et al., 1997): support comes from studies that have shown a positive correlation between brain activity in this region and reading accuracy and from investigations assessing the effects of reading interventions on reading skills and brain activations. Simos et al. (2002) used Magnetic Source Imaging (MSI) to find an increased activation in the left STG following a phonologically based reading intervention for dyslexic subjects, previously showing underactivations in this area. Shaywitz et al. (2004) also showed that a phonological intervention had led to an improvement in reading abilities and an increase in left hemisphere regions including, among others, the temporal gyrus. On the basis of the overactivation of the STG among subjects in D1 showing few differences relative to controls, and studies showing a correlation with reading intervention and increases in activation in this area, one possible explanation is that overactivation of the STG reflects cerebral compensatory mechanisms. However, it is difficult to clearly establish whether the STG overactivation is a neural marker of a subtype of dyslexia or whether it may be a consequence and compensatory response to dyslexia.

Finally, the study also showed abnormally low activation patterns in the cerebellum in D3 subjects relative to controls and D1. Although it is still rather unclear the role of the cerebellum in language and dyslexia, structural and functional abnormalities in this region have often been reported in studies on dyslexia. Some studies support a disruption of cerebellar pathways (Nicolson & Fawcett, 1990) in dyslexia, while a number of lesion studies have provided some evidence for a role of the cerebellum in linguistic deficits, reading errors, and depressed activation in the cerebellum in dyslexics readers when reading (Eckert et al., 2004). Anatomical studies also showed cerebellar anomalies in dyslexia, including right cerebellar anterior lobe and posterior lobe abnromalities, rightward gray matter asymmetry and reductions (Rae et al., 2002), and gray matter reduction in the left semilunar lobule (Eckert et al., 2003; Brown et al., 2001). Suggestions have been made supporting the an association between anomalies in the posterior cerebellar regions with language impairments. Interpretations regarding the cerebellum in dyslexia and language however vary according to investigators and viewpoints (Eckert et al., 2003), therefore, although the present study has revealed functional anomalies in the cerebellum during reading, it remains difficult to infer what role the cerebellum might play in dyslexia. Independently of its real involvement in DD, abnormally low cerebellar activations have been revealed in this study, and it is possible that cerebellar anomalies may account for a subtype of dyslexia.

In conclusion of the first section of the discussion, underactivation and overactivation differences between subgroups of dyslexic readers have been observed in this study, with D1 and D3 clearly diverging in brain activations, a fact that might have not been observed if the dyslexic sample was studied as a whole. There is a possibility that the different brain activations reflect neural markers specific to different subtypes of dyslexia. Once established that brain activations differed between the two subgroups during the same reading task, we aimed to establish whether the subgroups presented different behavioural traits and impairments. Put in other words, we attempted to see whether, in retrospect, we could predict brain activation on the basis of behavioural or vice versa.

Behavioural results indicated that D3 subjects performed statistically significantly worse on nonword repetition tasks (p=0.03) and showed a trend for worst performance in word spelling (p=0.06) as well. Both tasks tap into an assessment of the auditory input, thus suggesting a greater impairment in D3 in auditory processing. This is further supported by the functional results, showing lower activation in temporo-parietal regions considered important areas for auditory processing. The findings also reveal that the two subgroups showed no difference in age, gender, or performance IQ and in terms of word and nonword reading. The behavioural results are of particular significance because they show that a subgroup of dyslexic (D3) may be distinguishable on the basis of an auditory deficit, while the subgroups do not different in terms of IQ levels or word and nonword reading, differently from what other studies have reported (Shaywitz et al., 2003; Castle & Colthear, 1993).

A study by Shaywitz et al. (2003) assessed compensated dyslexics and persistently poor dyslexics. The results, showing a clear neural dissociation between the two subgroups, encouraged the authors to distinguish between two types of reading disability: a genetic type of dyslexia with IQ scores over 100 and a more environmental type with IQ scores below 100. The present study does not confirm these findings, as there were no differences in IQ scores between the subgroups identified. Nevertheless, as D1 seemed to show just overactivation in one brain region (STG) (previously associated with compensation following reading interventions by Simos et al., 2002) and no significant other activation differences relative to controls, as well as no significant worst behavioural performances compared to D3, suggestions could be made whether this subgroup may still represent a compensated sample of dyslexics, as the one studied by Shaywitz et al. (2003).

The study by Castle & Coltheart (1993), as well as other studies, showed a dissociation between dyslexic readers in word and nonword reading, encouraging the classical categorization of dyslexics into phonological and surface dyslexics. Despite our studying showing differences in auditory performances, the project showed no differences in performances in terms of word and nonword reading, thus failing to confirm the distinction of phonological and surface dyslexia.

Finally, despite differences in imaging results between D1 and D3, it is of importance to note that without the functional data and GMM, it would have been hard to distinguish D1 and D3 on the basis of behaviour alone. On the majority of the tasks, in fact, D1 and D3, although impaired relative to the controls, do not significantly differ from one another. D3 shows a trend for worse performance on most tasks, however, statistically, these differences did not reach significance (except for non-word repetition). It is possible that a larger sample may be able to reveal more statistically significant results. This is also true for performance on the auditory discrimination test, which did not reveal differences between the subgroups possibly due to missing data from half of subjects in both subgroups.

The behavioural data and analyses thus show few differences between subgroups, although still pinpointing to a major deficit in auditory performance characterizing D3 subjects. The deficit is further supported by functional data revealing abnormalities in auditory areas. Cluster analysis of behavioural data might help to group performance deficits and allow a comparison between functional and behavioural clusters. The partitioning of a data into subsets using cluster analyses is currently being carried out by the research team at the Institute of Neuroimaging and may yield to interesting results and further elucidation regarding functional deficits and their reflection on clusters of behavioural impairments.

In conclusion, identification of neural markers of DD would allow the basis for a more precise recognition of dyslexia and more targeted and effective therapeutic remedies. However, there is still a great deal of inconsistency and variability in the neuroimaging literature to allow the pinpointing of the precise neural systems involved in reading and dyslexia. One explanation for inconsistencies is the heterogeneity of dyslexia, which has encouraged research into identifying subtypes of dyslexia. The present study found 3 subgroups of dyslexics using a novel and unbiased approach based on a PCA/GMM method. Conventional ANOVA and the Mann-Whitney U test were then employed to compare two of the subgroups with each other (the third subgroup was excluded due to the small sample size) and revealed differences at the neural as well as behavioural level. D1 and D3 may represent two different subtypes of dyslexics with different brain anomalies and behavioural traits. D1 subjects, showing quite similar activation patterns to controls while reading and hyperactivation in the STG, may reflect a more compensated group of dyslexics. This could be further supported by superior mean performance levels on psychometric tests, showing also significant greater deficits in auditory tasks by D3 subjects compared to D1 subjects. Subject belonging to the D3 subgroup, may on the other hand reflect a type of dyslexia characterized by greater activation abnormalities and auditory short term memory deficits. Cluster analyses of behavioural data will further illuminate the correspondence between subgroups of dyslexic with different functional activations and behavioural deficits.

The present research project has important implications in the field of research on DD due to the inconsistencies of neuroimaging findings and the ongoing debate on finding reliable methods for subgrouping dyslexic readers. The PCA/GMM is an advantageous method with good potentials in solving the many questions in the literature regarding the existence of possible subgroups of dyslexics, while also solving the statistical difficulties regarding inter-subject variability and noise in neuroimaging in dyslexia. It is an unbiased classification method as it does not rely on any *a priori* knowledge upon which to classify the subjects. It also treats the inter-subject variability interfering with neuroimaging results on dyslexia by meaningful variance (Kherif et al., 2008). Limitations in the study include the small sample size and the wide range of ages of the population under investigation. Future research may then benefit from the use of this novel PCA/GMM approach to find subtypes of dyslexia while investigating larger samples of dyslexics and with less variability in terms of age. This may determine whether there are in fact more significant behavioural differences between the subjects and it would also allow the exploration of the subjects belonging to the D2 group, which in this study constituted an excessively small sample to use for analysis and comparisons.

The hopes and the attempts of our study to find a novel approach to subgroup dyslexics and examine neural and behavioural traits characterizing them is inspired by the final goal of identifying homogenous groups of dyslexics. Studying homogenous subtypes of dyslexia may allow consistencies in recognizing neural markers and behavioural deficits in order to effectively design remedial interventions for those affected by dyslexia.

V. REFERENCE

Beaulieu, C., Plewes, C., Paulson, L. A., Roy, D., Snook, L., Concha, L., & Phillips, L. (2005). Imaging brain connectivity in children with diverse reading ability. *Neuroimage., 25,* 1266-1271.

Brambati, S. M., Termine, C., Ruffino, M., Stella, G., Fazio, F., Cappa, S. F., & Perani, D. (2004). Regional reductions of gray matter volume in familial dyslexia. *Neurology, 63,* 742-745.

Brambati, S. M., Termine, C., Ruffino, M., Danna, M., Lanzi, G., Stella, G., Cappa, S. F., & Perani, D. (2006). Neuropsychological deficits and neural dysfunction in familial dyslexia. *Brain Res., 1113,* 174-185.

Brown, W.E., Eliez, S., Menon, V., Rumsey, J.M., White, C.D. & Reiss, A.L. (2001). Preliminary evidence of widespread morphological variations of the brain in dyslexia, *Neurology, 56*, 781–783.

Brunswick, N., McCrory, E., Price, C. J., Frith, C. D., & Frith, U. (1999). Explicit and implicit processing of words and pseudowords by adult developmental dyslexics: A search for Wernicke's Wortschatz? *Brain, 122 (Pt 10),* 1901-1917.

Castles, A. & Coltheart, M. (1993). Varieties of developmental dyslexia. *Cognition, 47,* 149-180.

Dehaene, L. Naccache, L. Cohen, D.L. Bihan, J.F. Mangin, J.B. Poline. (2001). Cerebral mechanisms of word masking and unconscious repetition priming. *Nat Neurosci., 4***,** 752–758.

Dejerine, J. (1891). Contribution a l'etude anatomo-pathologique et clinique des differentes varietes de cecite verbale. *Memoires de la Societe de Biologie*, *4,* 61–90.

Dejerine, J. (1891). Sur un cas de cécité verbale avec agraphie, suivi d'autopsie. *C R Société du Biologie*, *43*, 197–201.

Deutsch, G. K., Dougherty, R. F., Bammer, R., Siok, W. T., Gabrieli, J. D., & Wandell, B. (2005). Children's reading performance is correlated with white matter structure measured by diffusion tensor imaging. *Cortex, 41,* 354-363.

Dougherty, R. F., Ben-Shachar, M., Deutsch, G. K., Hernandez, A., Fox, G. R., & Wandell, B. A. (2007). Temporal-callosal pathway diffusivity predicts phonological skills in children. *Proc.Natl.Acad.Sci.U.S.A, 104,* 8556-8561.

Eckert, M. (2004). Neuroanatomical markers for dyslexia: a review of dyslexia structural imaging studies. *Neuroscientist., 10,* 362-371.

Eckert, M. A. & Leonard, C. M. (2000). Structural imaging in dyslexia: the planum temporale. *Ment.Retard.Dev.Disabil.Res.Rev., 6,* 198-206.

Finch, A. J., Nicolson, R. I., & Fawcett, A. J. (2002). Evidence for a neuroanatomical difference within the olivo-cerebellar pathway of adults with dyslexia. *Cortex, 38,* 529-539.

Francks, C., MacPhie, I. L., & Monaco, A. P. (2002). The genetic basis of dyslexia. *Lancet Neurol., 1,* 483-490.

Galaburda, A.M. & Kemper, T.L. (1979) Cytoarchitectonic abnormalities in dyslexia. *Annals of Neurology*, 6, 94–100.

Galaburda, A. M., Sherman, G. F., Rosen, G. D., Aboitiz, F., & Geschwind, N. (1985). Developmental dyslexia: four consecutive patients with cortical anomalies. *Ann.Neurol., 18,* 222-233.

Galaburda, A. M., Menard, M. T., & Rosen, G. D. (1994). Evidence for aberrant auditory anatomy in developmental dyslexia. *Proc.Natl.Acad.Sci.U.S.A, 91,* 8010-8013.

Heim, S., Tschierse, J., Amunts, K., Wilms, M., Vossel, S., Willmes, K., Grabowska, A., & Huber, W. (2008). Cognitive subtypes of dyslexia. *Acta Neurobiol.Exp.(Wars.), 68,* 73-89.

Henderson, V. W. (1986). Anatomy of posterior pathways in reading: A reassessment. *Brain and Language*, *29*, 119-133.

Hoeft, F., Hernandez, A., McMillon, G., Taylor-Hill, H., Martindale, J. L., Meyler, A., Keller, T. A., Siok, W. T., Deutsch, G. K., Just, M. A., Whitfield-Gabrieli, S., & Gabrieli, J. D. (2006). Neural basis of dyslexia: a comparison between dyslexic and nondyslexic children equated for reading ability. *J.Neurosci., 26,* 10700-10708.

Hoeft, F., Meyler, A., Hernandez, A., Juel, C., Taylor-Hill, H., Martindale, J. L., McMillon, G., Kolchugina, G., Black, J. M., Faizi, A., Deutsch, G. K., Siok, W. T., Reiss, A. L., Whitfield-Gabrieli, S., & Gabrieli, J. D. (2007). Functional and morphometric brain dissociation between dyslexia and reading ability. *Proc.Natl.Acad.Sci.U.S.A, 104,* 4234-4239.

Hoeft, F., Ueno, T., Reiss, A. L., Meyler, A., Whitfield-Gabrieli, S., Glover, G. H., Keller, T. A., Kobayashi, N., Mazaika, P., Jo, B., Just, M. A., & Gabrieli, J. D. (2007). Prediction of children's reading skills using behavioral, functional, and structural neuroimaging measures. *Behav.Neurosci., 121,* 602-613.

Interagency Committee on Learning Disabilities. (1987). Learning Disabilities: A report to Congress.

Jenner, A. R., Rosen, G. D., & Galaburda, A. M. (1999). Neuronal asymmetries in primary visual cortex of dyslexic and nondyslexic brains. *Ann.Neurol., 46,* 189-196.

Kherif, F., Josse, G., Seghier M.L., & Price, C.J. (2008). The main sources of inter-subject variability in neuronal activation for reading aloud. *J. Cogn Neurosci.*, (forthcoming).

Kibby, M. Y., Fancher, J. B., Markanen, R., & Hynd, G. W. (2008). A quantitative magnetic resonance imaging analysis of the cerebellar deficit hypothesis of dyslexia. *J.Child Neurol., 23,* 368-380.

King, W. M., Giess, S. A., & Lombardino, L. J. (2007). Subtyping of children with developmental dyslexia via bootstrap aggregated clustering and the gap statistic: comparison with the double-deficit hypothesis. *Int.J.Lang Commun.Disord., 42,* 77-95.

Klingberg, T., Hedehus, M., Temple, E., Salz, T., Gabrieli, J. D., Moseley, M. E., & Poldrack, R. A. (2000). Microstructure of temporo-parietal white matter as a basis for reading ability: evidence from diffusion tensor magnetic resonance imaging. *Neuron, 25,* 493-500.

Kronbichler, M., Hutzler, F., Staffen, W., Mair, A., Ladurner, G., & Wimmer, H. (2006). Evidence for a dysfunction of left posterior reading areas in German dyslexic readers. *Neuropsychologia, 44,* 1822-1832.

Kronbichler, M., Wimmer, H., Staffen, W., Hutzler, F., Mair, A., & Ladurner, G. (2008). Developmental dyslexia: gray matter abnormalities in the occipitotemporal cortex. *Hum.Brain Mapp., 29,* 613-625.

Lachmann, T., Berti, S., Kujala, T., & Schroger, E. (2005). Diagnostic subgroups of developmental dyslexia have different deficits in neural processing of tones and phonemes. *Int.J.Psychophysiol., 56,* 105-120.

Leonard, C. M., Voeller, K. K., Lombardino, L. J., Morris, M. K., Hynd, G. W., Alexander, A. W., Andersen, H. G., Garofalakis, M., Honeyman, J. C., Mao, J., & . (1993). Anomalous cerebral structure in dyslexia revealed with magnetic resonance imaging. *Arch.Neurol., 50,* 461-469.

Livingstone, M.S., Rosen, D. D., Drislane, F.W., & Galaburda, A.M. (1991). Physiological and anatomical evidence for a magnocellular defect in developmental dyslexia, *Proc. Natl. Acad. Sci. U. S. A.*, 88, 7943–7947.

Logan, G. (1988). Toward an instance theory of automatization. *Psychol Rev*, 95, 492–527.

Logan, G. (1997). Automaticity and reading: Perspectives from the instance theory of automatization. *Reading Writing Q: Overcoming Learn Disabil*, 13, 123–146.

Manis, F. R., Seidenberg, M. S., Doi, L. M., Bride-Chang, C., & Petersen, A. (1996). On the bases of two subtypes of developmental [corrected] dyslexia. *Cognition, 58,* 157-195.

Maurer, U., Brem, S., Bucher, K., Kranz, F., Benz, R., Steinhausen, H. C., & Brandeis, D. (2007). Impaired tuning of a fast occipito-temporal response for print in dyslexic children learning to read. *Brain, 130,* 3200-3210.

May, A., Hajak, G., Ganssbauer, S., Steffens, T., Langguth, B., Kleinjung, T., & Eichhammer, P. (2007). Structural brain alterations following 5 days of intervention: dynamic aspects of neuroplasticity. *Cereb.Cortex, 17,* 205-210.

McCrory, E., Frith, U., Brunswick, N., & Price, C. (2000). Abnormal functional activation during a simple word repetition task: A PET study of adult dyslexics. *J.Cogn Neurosci., 12,* 753-762.

McCrory, E. J., Mechelli, A., Frith, U., & Price, C. J. (2005). More than words: a common neural basis for reading and naming deficits in developmental dyslexia? *Brain, 128,* 261-267.

Meyler, A., Keller, T. A., Cherkassky, V. L., Lee, D., Hoeft, F., Whitfield-Gabrieli, S., Gabrieli, J. D., & Just, M. A. (2007). Brain activation during sentence comprehension among good and poor readers. *Cereb.Cortex, 17,* 2780-2787.

Morris, R., Stuebing, K., Fletcher, J., Shaywitz, S., Lyon, G., Shankweiler, D., Katz, L., Francis, D., Shaywitz, B. (1998). Subtypes of reading disability: variability around a phonological core. *J. Educ. Psychol., 90,* 347-373.

Murphy, L. & Pollatsek, A. (1994). Developmental dyslexia: heterogeneity without discrete subgroups. *Annals of Dyslexia., 44,* 120-146.

Nicolson, R.I. and Fawcett, A.J. (1990) Automaticity: a new framework for dyslexia research. *Cognition*, 35, 159–182.

Niogi, S. N. & McCandliss, B. D. (2006). Left lateralized white matter microstructure accounts for individual differences in reading ability and disability. *Neuropsychologia, 44,* 2178-2188.

Noppeney, U., Penny, W. D., Price, C. J., Flandin, G., & Friston, K. J. (2006). Identification of degenerate neuronal systems based on intersubject variability. *Neuroimage., 30,* 885-890.

Paulesu, E., Demonet, J. F., Fazio, F., McCrory, E., Chanoine, V., Brunswick, N., Cappa, S. F., Cossu, G., Habib, M., Frith, C. D., & Frith, U. (2001). Dyslexia: cultural diversity and biological unity. *Science, 291,* 2165-2167.

Phinney, E., Pennington, B. F., Olson, R., Filley, C. M., & Filipek, P. A. (2007). Brain structure correlates of component reading processes: implications for reading disability. *Cortex, 43,* 777-791.

Price C., Moore, C., & Frackowiak, R.S.J. (1996). The effect of varying stimulus rate and duration on brain activity during reading. *Neuroimage, 3,* 40–52.

Rae, C., Lee, M. A., Dixon, R. M., Blamire, A. M., Thompson, C. H., Styles, P., Talcott, J., Richardson, A. J., & Stein, J. F. (1998). Metabolic abnormalities in developmental dyslexia detected by 1H magnetic resonance spectroscopy. *Lancet, 351,* 1849-1852.

Rae, C., Harasty, J. A., Dzendrowskyj, T. E., Talcott, J. B., Simpson, J. M., Blamire, A. M., Dixon, R. M., Lee, M. A., Thompson, C. H., Styles, P., Richardson, A. J., & Stein, J. F. (2002). Cerebellar morphology in developmental dyslexia. *Neuropsychologia, 40,* 1285-1292.

Ramus, F., Rosen, S., Dakin, S. C., Day, B. L., Castellote, J. M., White, S., & Frith, U. (2003). Theories of developmental dyslexia: insights from a multiple case study of dyslexic adults. *Brain, 126,* 841-865.

Rumsey, J. M., Nace, K., Donohue, B., Wise, D., Maisog, J. M., & Andreason, P. (1997). A positron emission tomographic study of impaired word recognition and phonological processing in dyslexic men. *Arch.Neurol., 54,* 562-573.

Rumsey, J. M., Donohue, B. C., Brady, D. R., Nace, K., Giedd, J. N., & Andreason, P. (1997). A magnetic resonance imaging study of planum temporale asymmetry in men with developmental dyslexia. *Arch.Neurol., 54,* 1481-1489.

Rumsey, J. M., Horwitz, B., Donohue, B. C., Nace, K., Maisog, J. M., & Andreason, P. (1997). Phonological and orthographic components of word recognition. A PET-rCBF study. *Brain, 120 (Pt 5),* 739-759.

Rumsey, J. M. (1998). Brain imaging of reading disorders. *J.Am.Acad.Child Adolesc.Psychiatry, 37,* 12.

Rumsey, J. M., Horwitz, B., Donohue, B. C., Nace, K. L., Maisog, J. M., & Andreason, P. (1999). A functional lesion in developmental dyslexia: left angular gyral blood flow predicts severity. *Brain Lang, 70,* 187-204.

Salmelin, R., Service, E., Kiesila, P., Uutela, K., & Salonen, O. (1996), Impaired visual word processing in dyslexia revealed with magnetoencephalography. *Ann Neurol., 40,* 157–162.

Shaywitz, B. A., Shaywitz, S. E., Pugh, K. R., Mencl, W. E., Fulbright, R. K., Skudlarski, P., Constable, R. T., Marchione, K. E., Fletcher, J. M., Lyon, G. R., & Gore, J. C. (2002). Disruption of posterior brain systems for reading in children with developmental dyslexia. *Biol.Psychiatry, 52,* 101-110.

Shaywitz, B. A., Lyon, G. R., & Shaywitz, S. E. (2006). The role of functional magnetic resonance imaging in understanding reading and dyslexia. *Dev.Neuropsychol., 30,* 613-632.

Shaywitz, B. A., Skudlarski, P., Holahan, J. M., Marchione, K. E., Constable, R. T., Fulbright, R. K., Zelterman, D., Lacadie, C., & Shaywitz, S. E. (2007). Age-related changes in reading systems of dyslexic children. *Ann.Neurol., 61,* 363-370.

Shaywitz, S. E. (1998). Dyslexia. *N.Engl.J.Med., 338,* 307-312.

Shaywitz, S. E., Shaywitz, B. A., Pugh, K. R., Fulbright, R. K., Constable, R. T., Mencl, W. E., Shankweiler, D. P., Liberman, A. M., Skudlarski, P., Fletcher, J. M., Katz, L., Marchione, K. E., Lacadie, C., Gatenby, C., & Gore, J. C. (1998). Functional disruption in the organization of the brain for reading in dyslexia. *Proc.Natl.Acad.Sci.U.S.A, 95,* 2636-2641.

Shaywitz, S. E. & Shaywitz, B. A. (2003). The science of reading and dyslexia. *J.AAPOS., 7,* 158-166.

Shaywitz, S. E., Shaywitz, B. A., Fulbright, R. K., Skudlarski, P., Mencl, W. E., Constable, R. T., Pugh, K. R., Holahan, J. M., Marchione, K. E., Fletcher, J. M., Lyon, G. R., & Gore, J. C. (2003). Neural systems for compensation and persistence: young adult outcome of childhood reading disability. *Biol.Psychiatry, 54,* 25-33.

Shaywitz, S. E. & Shaywitz, B. A. (2003). Dyslexia (specific reading disability). *Pediatr.Rev., 24,* 147-153.

Shaywitz, S. E., Gruen, J. R., & Shaywitz, B. A. (2007). Management of dyslexia, its rationale, and underlying neurobiology. *Pediatr.Clin.North Am., 54,* 609-23, viii.

Silani, G., Frith, U., Demonet, J. F., Fazio, F., Perani, D., Price, C., Frith, C. D., & Paulesu, E. (2005). Brain abnormalities underlying altered activation in dyslexia: a voxel based morphometry study. *Brain, 128,* 2453-2461.

Simos, P.G., Fletcher, J.M., Bergman, E., Breier, J.I., Foorman, B.R., Castillo, E.M. (2002). Dyslexia-specific brain activation profile becomes normal following successful remedial training. *Neurology, 58*, 1203–1213.

Stanovich, K. E., Siegel, L. S., & Gottargo, A. (1997). Converging evidence for phonological and surface subtypes of reading disability. *J. Educ. Psychol., 89,* 114-127.

Vinckenbosch, E., Robichon, F., & Eliez, S. (2005). Gray matter alteration in dyslexia: converging evidence from volumetric and voxel-by-voxel MRI analyses. *Neuropsychologia, 43,* 324-331.

von Plessen, K., Lundervold, A., Duta, N., Heiervang, E., Klauschen, F., Smievoll, A. I., Ersland, L., & Hugdahl, K. (2002). Less developed corpus callosum in dyslexic subjects--a structural MRI study. *Neuropsychologia, 40,* 1035-1044.

Williams, J. & O'Donovan, M. C. (2006). The genetics of developmental dyslexia. *Eur.J.Hum.Genet., 14,* 681-689.

Wolf, M., Feil, C., Lotz, R., & Boddle, K. (1994). Towards a more universal understanding of the developmental dyslexias: the contributions of orthographic factors. In V.W. Berninger (Ed.), *The Varieties of Orthographic Knowledge, 1,* 137-171. Dordrecht, The Netherlands: Kluwer Academics.

Zadina, J. N., Corey, D. M., Casbergue, R. M., Lemen, L. C., Rouse, J. C., Knaus, T. A., & Foundas, A. L. (2006). Lobar asymmetries in subtypes of dyslexic and control subjects. *J.Child Neurol., 21,* 922-931.

VI. APPENDIX

IQ ASSESSMENT—WESCHLER ADULT INTELLIGENCE SCALE (WAIS III)	
SUBTESTS	
VERBAL IQ ASSESSMENT	***PERFORMANCE IQ ASSESSMENT***
VOCABULARY	PICTURE COMPLETION
SIMILARITIES	DIGIT SYMBOL CODING
ARYTHMETIC	BLOCK DESIGN
DIGIT SPAN	MATRIX REASONING
INFORMATION	PICTURE ARRANGEMENT
COMPREHENSION	

Appendix 1. Verbal and non-verbal IQ measures administered to each participant in the study as part of the Wechsler Adult Intelligence Scale (WAIS III)

	TESTS	DESCRITPION	PURPOSE OF TESTS
SPELLING (*WRAT*)	*Word& Nonword spelling*	A spelling test consisting of writing dictated words and nonwords	Assess spelling accuracy
READING	*WRAT (Wide Range Achievement Test)*	A reading test consisting words that the examinee is asked to name or pronounce	Assess accuracy and reaction times for reading aloud skills
	WTAR (Weschler Test of Adult Reading)	A reading test consisting of pronouncing irregularly spelled words	Assess accuracy and reaction times for reading aloud skills
	NART (National Reading Test)	A reading test consisting of "irregular" words that violate standard spelling-to-sound correspondence rules	Assess accuracy and reaction times for reading aloud skills
	Non-word reading	A reading test consisting of nonword reading	Assess accuracy and reaction times for reading aloud skills

PhAB (Phonological Assessment Battery)	*Picture Naming*	Requires the subject to name aloud a series of pictures of objects as fast and accurately as possible while the person is being timed	Assess phonological skills
	Digit Naming	Requires the subject to read aloud a string of numbers in a row as fast and accurately as possible while the person is being timed.	Assess phonological skills
SPOONERISMS		Requires the subject to swap over the beginning letter of two words; e.g. the words RED/PEN becomes PED/REN	Assessing phonological skills
NONWORD REPETITION		Repetition of non-words presented to the examinee	Assess phonological processing
LEXICAL DECISION	*Nonword Trails (1 & 2)*	The subject is required to decide whether non-existent words presented on a computer screen are spelled correctly	Assess spelling
	Word Trials (1 & 2)	The subject is required to decide whether real words presented on a computer screen are spelled correctly (e.g. rayle)	Assess spelling
NONWORD DECISION	*Trials 1, 2, & 3*	The subject is required to decide whether orally-presented nonwords sound like real words (e.g. fenk)	Assess ability to access the sounds of words
BOSTON NAMING		A test consisting of naming pictures of objects	Assess the ability to name pictures of objects through spontaneous responses and need for various types of cueing

PALPA (Psycholinguistic Assessment of Language Processes in Aphasia)	*Nonword*	Requires the subject to listen to pairs of nonwords at a time through headphones and decide if the two nonwords are the same or not	Assess auditory perception & discrimination
	Word	Requires the subject to listen to pairs of words through headphones and decide if the two words are the same or not	Assess auditory perception & discrimination
	Rhyme	Look at pictures of two items and decide whether the name of the two pictures rhyme	Assess ability to access the name of a picture, hold it in memory and match it to the name of a second picture

Appendix 2. Name, description and purpose of the psychometric tests administered to each participant in the study